Palladium-catalyzed enantioselective conjugate addition of arylboronic acids

Gini, F; Hessen, B; Minnaard, AJ

Published in:
Organic letters

DOI:
10.1021/ol052222d

Publication date:
2005

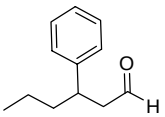
Palladium Catalyzed Enantioselective Conjugate Addition of Boronic Acids

Francesca Gini, Bart Hessen, Adriaan J.Minnaard*

Department of Organic Chemistry and Molecular Inorganic Chemistry,
Stratingh Institute, University of Groningen,
Nijenborgh 4, 9747 AG, Groningen, The Netherlands

General Experimental.

^{1}H NMR spectra were recorded at 300 or 400 MHz with $CDCl_3$ as solvent. ^{13}C NMR spectra were obtained at 75.4 or 100.6 MHz in $CDCl_3$, (Varian VXR300 or AMX400 spectrometers). Chemical shifts were determined relative to the residual solvent peaks (δ = 7.26 ppm for hydrogen, δ = 77.0 for carbon). Data are reported as follows: chemical shifts, integration, multiplicity (s = singlet, d = doublet, t =triplet, q = quartet, br = broad, m = multiplet) and coupling constants (Hz). Mass spectra were recorded on a AEI-MS-902 mass spectrometer. Enantioselectivities were determined by capillary GC analysis (Chiraldex G-TA column (30 m x 0.25 mm) or Chiraldex α-TA column (30 m x 0.25 mm)) using a flame ionization detector and compared with the racemic 1,4 addition products. HPLC analysis was carried out on a Shimadzu LC-10AD*VP* HPLC equipped with a Shimadzu SPD-M10A*VP* diode array detector. Conversion of the reaction was determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Thin-layer chromatography (TLC) was performed on silica gel, components were visualized by staining with $KMnO_4$ reagent. Flash chromatography was performed on silica gel. All reactions were carried out under nitrogen atmosphere using dried glassware. All solvents were dried and distilled before use according to standard procedures.
Ligand **L*$_1$** was provided by Solvias, **L*$_2$** was purchased from Fluka and **L*$_3$, L*$_4$, L*$_5$** were purchased from Strem. All starting materials and products have been described in the literature.
Racemic **3k** was prepared by reaction of **1d** with phenylmagnesium bromide in dry THF at 0 °C in the presence of CuCl (3 mol %) and TMSCl (1.1 eq.).
Both enantiomers of **3l** were synthesized by the asymmetric rhodium/phosphoramidite catalyzed addition of phenylboronic acid to **1e** according to reported procedure.[1]
Racemic **3m** was prepared by reaction of *trans*-4-phenyl-3-buten-2-one with *n*-butylmagnesium bromide in dry Et_2O at 0 °C in the presence of stoichiometric CuI.
The Heck coupling product **4** was synthesized by reaction of **1h** with iodobenzene in NMP in the presence of $Pd(OAc)_2$ (0,05 mol %).[2]

Synthesis of racemic 3-Phenylhexanal (3n).[3] 

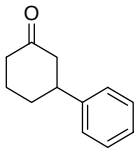
A solution of Et_3N (5 mmol, 0.7 mL) in hexane (2.5 mL) was added dropwise to a solution of cinnamoyl chloride (4.5 mmol, 750 mg) and EtSH (4.5 mmol, 0.34 mL) in hexane (10 mL) at 0°C. The mixture was stirred overnight and allowed to reach room temperature. The precipitate was filtered off and washed with hexane/Et_2O (1:1). Purification of the crude by column chromatography (pentane/ Et_2O = 50:1) afforded the (E)-3-phenyl-thioprop-2-ene-oic acid (S)-ethyl ester as colorless oil (563 mg, 2.9 mmol, 65%). The ethyl ester was dissolved in dry Et_2O (20 mL) in the presence of CuI (100 mol %, 2.9 mmol, 552 mg) and *n*-PrMgBr (3.09 M in Et_2O, 1.2 eq., 3.5 mmol, 1.2 mL) was added dropwise at 0 °C. After stirring for 30 min at rt, NH_4Cl aq. was added dropwise,

the organic layer concentrated and then the crude was purified by column chromatography (pentane/ Et_2O = 50:1) to isolate the 1,4-addition product 3-phenyl-thiohexanoic acid (S)-ethyl ester (130 mg, 0.6 mmol, 20%). The product was dissolved in CH_2Cl_2 (1 mL) and 10% Pd-C (5 mol %, 30 mg) was added at rt under nitrogen. After addition of Et_3SiH (3 eq., 1.8 mmol, 0.3 mL) the mixture was stirred at rt overnight and then filtered over Celite and washed with CH_2Cl_2. Purification by column chromatography (pentane/ Et_2O =100:1) afforded the racemic 3-phenylhexanal **3n** as colorless oil (40 mg, 0.23 mmol, 41%).

General procedure for the palladium catalyzed asymmetric conjugate addition of arylboronic acids.

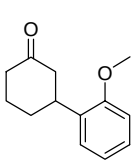
In a flame dried Schlenk tube equipped with septum and stirring bar, $Pd(O_2CCF_3)_2$ (5 mol %, 5 μmol, 1.66 mg) and ligand $\mathbf{L_3}$ (5.5 mol %, 5.5 μmol, 1.68 mg) were dissolved in dry THF (1.0 mL) and stirred under nitrogen at room temperature for 10 min. Arylboronic acid (3 eq., 0.30 mmol) was added, followed by the addition of enone **1** (0.1 mmol). After the addition of H_2O (0.1 mL) the mixture was degassed by alternating vacuum-nitrogen cycles and then heated to 50 °C. When the reaction was complete according to TLC analysis, the mixture was cooled down to room temperature and aqueous $NaHCO_3$ sat. solution was added. The organic phase was separated and the resulting aqueous layer was extracted with Et_2O. The combined organic phases were filtered over a plug of silica, dried on $MgSO_4$, concentrated and purified by flash chromatography (Et_2O/pentane) to yield the corresponding products **3**. The composition and the conversion in the crude mixture were determined by NMR and GC-MS analysis.

(R)-3-Phenyl-cyclohexanone (3a)[4]



Ketone **3a** was obtained after purification by flash chromatography (eluent pentane/Et2O 5:1) in 80% yield, 98% ee. ^{1}H-NMR δ 1.69-1.86 (2H, m), 2.02-2.14 (2H, m), 2.29-2.58 (4H, m), 2.93-2.99 (1H, m), 7.17- 7.31 (5H, m); ^{13}C-NMR δ 211.5, 144.3, 128.7, 126.7, 126.6, 48.9, 44.7, 41.2, 32.8, 25.5. MS, *m/z* (%): 174 (M+, 100), 131 (68.4), 117 (86.8). HRMS for $C_{12}H_{14}O$ calcd 174.104, found 174.105. E.e. was determined by HPLC analysis, Chiralpak AD column, Heptane/*i*-PrOH 99:1, detection at 209 nm, retention times: 12.1 (Min) / 13.8 (Maj) min.

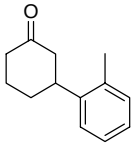
(+)-(R)-3-(2-Methoxyphenyl)-cyclohexanone (3b)[5]



Ketone **3b** was obtained after purification by flash chromatography (eluent pentane/Et2O 5:1) in 80% yield, 99% ee. ^{1}H-NMR δ 1.75-2.14 (4H, m), 2.32-2.60 (4H, m), 3.37-3.48 (1H, m), 3.81 (3H, s), 6.85-6.95 (2H, m), 7.16-7.26 (2H, m). MS, *m/z* (%): 204 (M+, 91.9), 147 (100), 91. HRMS for $C_{13}H_{16}O_2$ calcd 204.115, found 204.116. E.e. was determined by chiral

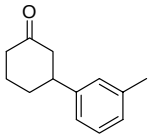
HPLC analysis, Chiralcel OD column, Heptane/*i*-PrOH 95:5, detection at 210 nm, retention times: 8.1 (Min) / 9.0 (Maj) min.

(+)-(R)-3-(2-Methylphenyl)-cyclohexanone (3c)[5]



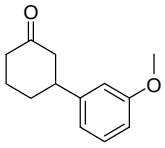
Ketone **3c** was obtained from the reaction of **1a** with **2c** in quantitative yield without further purification in 99% ee. ^{1}H-NMR δ 1.75-1.82 (2H, m), 1.94-1.98 (1H, m), 2.11-2.15 (1H, m), 2.28 (3H, s), 2.35-2.48 (4H, m), 3.11-3.22 (1H, m), 7.11-7.21 (4H, m). MS, *m/z* (%): 188 (M+, 100), 145 (92.4), 131 (81.3). HRMS for $C_{13}H_{16}O$ calcd 188.120, found 188.121. E.e. was determined by chiral HPLC analysis, Chiralpak AD column, Heptane/*i*-PrOH 99:1, detection at 209 nm, retention times: 9.3 (Min) / 11.63 (Maj) min.

(+)-3-(3-Methylphenyl)-cyclohexanone (3d)[5]



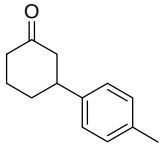
Ketone **3d** was obtained from the reaction of **1a** with **2d** in quantitative yield without further purification in 97% ee. ^{1}H-NMR δ 1.68-1.83 (2H, m), 2.01-2.13 (2H, m), 2.30 (3H, s), 2.34-2.53 (4H, m), 2.89-2.92 (1H, m), 6.96-7.02 (3H, m), 7.15-7.21 (1H, m). MS, *m/z* (%): 188(M+, 100), 145 (52.6), 131 (85). HRMS for $C_{13}H_{16}O$ calcd 188.120, found 188.121. E.e. was determined by chiral HPLC analysis, Chiralpak OD column, Heptane/*i*-PrOH 99:1 grad. 90/10, detection at 209 nm, retention times: 11.37 (Min) / 13.61 (Maj) min.

(+)-3-(2-Methoxyphenyl)-cyclohexanone (3e)[5]



Ketone **3e** was obtained after purification by flash chromatography (eluent pentane/Et_2O 5:1) in 98% yield, 98% ee. ^{1}H-NMR δ 1.65-1.82 (2H, m), 2.01-2.13 (2H, m), 2.29-2.58 (4H, m), 2.89-2.97 (1H, m), 3.75 (3H, s), 6.71-6.78 (3H, m), 7.17-7.23 (1H, m). MS, *m/z* (%): 204 (M+, 100), 163 (29.3), 134 (51.0). HRMS for $C_{13}H_{16}O_2$ calcd 204.115, found 204.116. E.e. was determined by chiral HPLC analysis, Chiralcel OD column, Heptane/*i*-PrOH 99:1, detection at 210 nm, retention times: 33.7 (Min) / 38.3 (Maj) min.

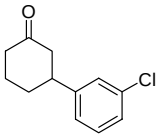
3-*p*-Tolyl-cyclohexanone (3f)[4]



Ketone **3f** was obtained after purification by flash chromatography (eluent pentane/Et_2O 5:1) in 90% yield, 97% ee. ^{1}H-NMR δ 1.70-1.81 (2H, m), 2.00-2.13 (2H, m), 2.29 (3H, s), 2.30-2.55 (4H, m), 2.89-2.96 (1H, m), 7.06-7.22 (4H, m). ^{13}C-NMR δ 211.05, 141.4, 136.2, 129.3, 126.4, 49.1, 44.4, 41.2, 32.9, 25.6, 20.96. MS, *m/z* (%): 188 (M+, 51.9), 145 (25.5), 131 (100). HRMS for $C_{13}H_{16}O$ calcd 188.120, found 188.121. E.e. was determined by chiral HPLC analysis, Chiralpak AD column, Heptane/*i*-PrOH 98:2, detection at 209 nm, retention times: 7.3 (Min) / 7.65 (Maj)

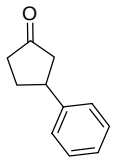
min or by chiral GC, Chiraldex G-TA column (30 m x 0.25 mm) 140 °C, retention times: 52.9 (Maj) / 54.6 (Min) min.

3-(3-Methylphenyl)-cyclohexanone (3h)[6]



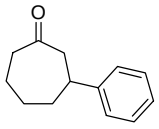
2-Cyclohexenone gave 60% of conversion in **3h** that was obtained after purification by flash chromatography (eluent pentane/Et_2O 5:1) in 40% yield, 98% ee. ^{1}H-NMR δ 1.66-1.96 (2H, m), 2.02-2.12 (2H, m), 2.27-2.56 (4H, m), 2.88-2.96 (1H, m), 7.01-7.14 (1H, m), 7.15-7.22 (3H, m); ^{13}C-NMR δ 210.4, 146.3, 134.5, 129.9, 126.9, 126.8, 124.8, 48.6, 44.4, 41.1, 32.5, 25.4. E.e. was determined by chiral HPLC analysis, Chiralcel AD column, Heptane/*i*-PrOH 98:2, detection at 254 nm, retention times: 8.8 (Min) / 9.9 (Maj) min.

(+)-(R)-3-Phenyl-cyclopentanone (3i)[4]



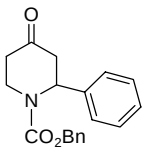
Ketone **3i** was obtained following the general procedure at room temperature after purification by flash chromatography (eluent pentane/Et_2O 5:1) in 75% yield, 82% ee. ^{1}H-NMR δ 1.89-1.97 (1H, m), 2.21-2.46 (4H, m), 2.63 (1H, dd, *J* = 6.96 and 17.96 Hz), 3.34-3.41 (1H, m), 7.19-7.32 (5H, m); ^{13}C-NMR δ 218.5, 142.9, 128.6, 126.7, 45.7, 42.5, 38.8, 31.1. MS, *m/z* (%): 160 (M+, 82.8), 117 (37.6), 104 (100). HRMS for $C_{11}H_{12}O$ calcd 160.0888, found 160.0896. E.e. was determined by chiral GC, Chiraldex α-TA column (30 m x 0.25 mm) 140°C, retention times: 16.8 (Min) / 18.6 (Maj) min.

(+)-(R)-3-Phenyl-cycloheptanone (3j)[4]



Ketone **3j** was obtained after purification by flash chromatography (eluent pentane/Et_2O 5:1) in 53% yield, 86% ee. ^{1}H-NMR δ 1.43-1.47 (1H, m), 1.63-1.72 (2H, m), 1.93-2.06 (3H, m), 2.53-2.62 (3H, m), 2.85-2.92 (2H, m), 7.12-7.27 (5H, m); ^{13}C-NMR δ 213.3, 146.9, 128.6, 126.4, 51.2, 43.9, 42.7, 39.2, 29.7, 24.2. MS, *m/z* (%): 188 (M+, 100), 130 (57.4), 104 (82.8). HRMS for $C_{13}H_{16}O$ calcd 188.120, found 188.121. E.e. was determined by chiral HPLC analysis, Chiralcel OD column, Heptane/*i*-PrOH 95:5, detection at 210 nm, retention times: 6.7 (Min) / 7.2 (Maj) min.

(+)-(R)-N-Carbobenzyloxy-2-Phenyl-4-piperidone (3l)[7]



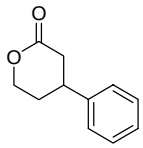
Piperidone **3l** was obtained according to the general procedure performing the reaction at 70 °C after purification by flash chromatography (eluent pentane/Et_2O 1:1) in 60% yield, > 99% ee. ^{1}H-NMR δ 2.28-2.34 (1H, d, *J* = 16.11 Hz), 2.42-2.79 (1H, m), 2.80-2.84 (1H, dd, *J* = 3.66 and 6.59 Hz), 2.93 (1H, d, *J* = 15.38 Hz), 3.13 (1H, t, *J* = 11.35 Hz), 4.21 (1H, bs), 5.11-5.21 (2H, m), 5.78 (1H, bs), 7.19-7.33 (10H, m); ^{13}C-NMR δ 207.2, 155.3, 139.6, 136.2, 128.8, 128.5, 128.2, 127.9, 126.7, 67.8, 54.6, 44.1, 40.5, 38.9.

MS, *m/z* (%): 309 (M+), 218 (43), 132, 91 (100). E.e. was determined by chiral HPLC analysis, Chiralcel OD-H column, Heptane/*i*-PrOH 90:10, detection at 210 nm, retention times: 26.6 (min, not visible) / 31.6 (Maj) min.

General procedure for the asymmetric conjugate addition of phenylboroxine.

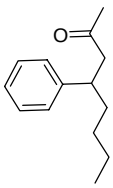
In a flame dried Schlenk tube equipped with septum and stirring bar, $Pd(O_2CCF_3)_2$ (5 mol %, 5 μmol, 1.66 mg) and ligand **L$_3$** (5.5 mol %, 5.5 μmol, 1.68 mg) were dissolved in dry THF (1.0 mL) and stirred under nitrogen at room temperature for 10 min. Phenylboroxine (3 eq., 0.30 mmol, 94 mg) was added, followed by the addition of enone **1** (0.1 mmol). The resulting mixture was heated to 50 °C and 0.4 mL of a 20 vol % solution of water in THF was added slowly by syringe pump (0.1 mL/h). After the addition, stirring was continued overnight and then the reaction was cooled down to room temperature, diluted with Et_2O and filtered over a plug of silica. The crude was dried, concentrated and purified by flash chromatography (Et_2O/pentane) to yield the corresponding products **3**. The composition and the conversion in the crude mixture were determined by NMR and GC-MS analysis.

(+)-(S)-4-Phenyl-tetrahydro-2H-pyran-2-one (3k)[8]



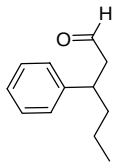
Pyranone **3k** was obtained after purification by flash chromatography (eluent pentane/Et_2O 3:2) in 75% yield, 94% ee. ^{1}H-NMR δ 1.97-2.02 (1H, m), 2.11-2.15 (1H, m), 2.59 (1H, dd, *J* = 10.6 and 17.6 Hz), 2.88 (1H, ddd, *J* = 1.8, 5.9 and 17.6 Hz), 3.18-3.21 (1H, m), 4.32-4.38 (1H, m), 4.43-4.48 (1H, m), 7.16-7.34 (5H, m). MS, *m/z* (%): 176 (M+, 100), 117 (85.8), 104 (82.4). HRMS for $C_{11}H_{12}O_2$ calcd 176.084, found 176.085. E.e. was determined by chiral GC, Chiraldex G-TA column (30 m x 0.25 mm), 170 °C, retention times: 123.0 (Min) / 124.1 (Maj) min.

4-Phenyl-2-octanone (3m)[9]



3-octen-2-one **1f** gave 60% conversion in ketone **3m** that was obtained after purification by flash chromatography (eluent pentane/Et_2O 100:1) in 45 % yield and 82% ee. ^{1}H-NMR δ 0.78 (3H, t, *J* = 7.3), 1.04-1.26 (4H, m), 1.50-1.59 (2H, m), 1.96 (3H, s), 2.62-2.68 (2H, m), 3.03-3.08 (1H, m), 7.07-7.26 (5H, m); ^{13} C-NMR δ 207.9, 144.5, 128.4, 127.4, 126.2, 50.9, 41.2, 36.1, 30.6, 29.5, 22.5, 13.9. MS, *m/z* (%): 204 (M+, 17.2), 147 (80.2), 91 (100). HRMS for $C_{14}H_{20}O$ calcd 204.151, found 204.152. E.e. was determined by chiral HPLC analysis, Chiralcel OB-H column, Heptane/*i*-PrOH 99:1, detection at 210 nm, retention times: 13.6 (Maj) / 19.3 (Min) min.

3-Phenyl-hexanal (3n)[6]



trans-2-hexenal gave 42% conversion in aldehyde **3n** that was obtained after purification by flash chromatography (eluent pentane/ Et_2O 100 : 1) in 30% yield and 50% ee. ^{1}H-NMR δ 0.82 (3H, t, *J* = 7.3 Hz), 1.11-1.18 (2H, m), 1.55-1.61 (2H, m), 2.67 (2H, dd, *J* = 1.83 and 6.97 Hz), 3.12-3.16 (1H, m), 7.13-7.28 (5H, m), 9.62 (1H, t, *J* = 2.2 Hz); ^{13}C-NMR δ 202.1, 143.9, 128.6, 127.4, 126.5, 50.5, 39.8, 38.8, 20.4, 13.9. MS, *m/z* (%): 176 (M+, 8.1), 132 (57.9), 107 (79.9), 91 (100). HRMS for $C_{12}H_{16}O$ calcd 176.120, found 176.123. E.e. was determined by chiral HPLC analysis, Chiralcel OD-H column, Heptane/*i*-PrOH 98:2, detection at 210 nm, retention times: 20.9 (Min) / 31 (Maj) min.

References.

[1] Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 2433.

[2] de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285.

[3] Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta* **2004**, *37*, 87 and references cited therein; Des Mazery, R.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005,** *127*, 9966.

[4] Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5579. For the absolute configuration determination of **3h** see: Defieber, C.; Paquin, J-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *21*, 3873.

[5] Boiteau, J.; Imbos, R.; Minnaard; A. J., Feringa B. L. *Org. Lett.* **2003**, *5*, 681. For the absolute configuration determination of **3b** see: Defieber, C.; Paquin, J-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *21*, 3873. For the absolute configuration determination of **3c** see: Hayashi, T.; Tokunaga, N.; Yoshida, K.; Han, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 12102.

[6] Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.

[7] Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240.

[8] Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047.

[9] Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47,* 119.